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| 09/243,030   | 02/03/1999  | MICHAEL GERARD TOVEY | TOVEY1A                       | 1869             |
| 1444 7590 06/25/2008<br>BROWDY AND NEIMARK, P.L.L.C.<br>624 NINTH STREET, NW<br>SUITE 300<br>WASHINGTON, DC 20001-5303 |             |                      | EXAMINER<br>ANDERSON, JAMES D |                  |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary****Application No.**

09/243,030

**Applicant(s)**

TOVEY, MICHAEL GERARD

**Examiner**

JAMES D. ANDERSON

**Art Unit**

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**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 04 March 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 22-58 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 22-58 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
- Paper No./Mail Date: \_\_\_\_\_

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

#### ***Claims 22-58 are presented for examination***

Applicants' amendment filed 3/4/2008 has been received and entered into the application. Accordingly, claims 22-24, 30-32, 36-40, 46-48, 52, and 58 have been amended.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

#### ***Response to Arguments***

Applicant's arguments filed 3/4/2008 have been fully considered but they are not persuasive. Applicants present the following arguments with respect to the rejections set forth in the previous Office Action.

With respect to the 35 U.S.C. 112, 1<sup>st</sup> paragraph rejection of claims 22-58 as lacking enablement for the treating viral infections other than rhinoviral infections with oromucosally administered interferon, Applicants argue that the references cited by the Examiner (Smith, two Hayden references, and Santus) do not cast doubt on the "disclosed utility" of the present invention relating to all types of viral infections. In this regard, Applicants argue that Smith and both Hayden references treat viruses directly with interferon, not indirectly as in the present invention. However, Smith teaches that intranasally administered interferon does not protect against dissemination of hepatitis virus to other organs and further than systemic infection was not affected by intranasal interferon treatment. Hayden teaches that intranasal administration of

interferon is not effective in treating naturally occurring common colds. As such, if intranasal administration of interferon is not effective to directly treat these viral infections, it is certainly not predictable that intranasal administration of interferon that does not involve direct action of interferon on virally infected cells and does not result in biologically active interferon entering the bloodstream will be effective to treat "a viral infection" (e.g., influenza, viral encephalitis, genital herpes, hepatitis, and HIV) as broadly recited in the instant claims. As discussed in the previous Office Action, Applicants' only working example shows that oromucosal administration to mice protected mice from an EMCV infection. There is no working example of oromucosal administration of any interferon that does not involve direct action of interferon on virally infected cells and does not result in biologically active interferon entering the bloodstream treating any viral infection. Applicant cites several papers relating to the present invention and asserts that the teaching of these papers supports the enablement of the present claims. These articles primarily focus on the same example as that shown in the instant specification, i.e., that oromucosal administration of interferon protects mice infected with a lethal dose of EMCV (Eid et al. (1999), Tovey et al. (1999), and Schellekens et al. (2001)). Tovey et al. provides additional data with respect to vesicular stomatitis virus and varicella zoster virus. However, the Examiner is not persuaded that the effect of oromucosal administration of interferon to mice challenged with EMCV, vesicular stomatitis virus, or varicella zoster virus is predictive of the treatment of other viral infections such as influenza, viral encephalitis, genital herpes, hepatitis, and HIV as broadly encompassed by the claims. In other words, there is no evidence of record that oromucosal administration of interferon in a manner that does not involve direct action of interferon on virally infected cells and does not

result in biologically active interferon entering the bloodstream will be effective to treat "a viral infection" (e.g., influenza, viral encephalitis, genital herpes, hepatitis, and HIV) as recited in the instant claims.

***Claim Rejections - 35 USC § 112 (2<sup>nd</sup> Paragraph)***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-24 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 23 and 24 depend from claim 37, which recites administration of "a unit dose" of interferon. Claims 39 and 40 depend from claim 36, which also recite administration of "a unit dose" of interferon. Claims 23 and 39 recite the limitation wherein the "unit dose" of interferon is "delivered in a plurality of smaller amounts over a period of time". Claims 24 and 40 recite the limitation wherein the amount of interferon is administered "continuously over a period of time". Claims are indefinite because a unit dose as recited in claims 36 and 37 is recognized in the specification and in the prior art as a single dose. For example, see page 6, lines 5-10 of the instant specification wherein Applicant makes a clear distinction between a "single dose" (i.e., a unit dose) and a "plurality of smaller doses over a period of time" or "continuously over a period of time". As such, it is not clear how one can administer a unit dose (i.e., a single dose) in multiple doses or continuously over a period of time as recited in claims 23-24 and 39-40.

***Claim Rejections - 35 USC § 112 (1<sup>st</sup> Paragraph)***

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a rhinoviral infection or EMCV infection with recombinant interferon- $\alpha_2$ , does not reasonably provide enablement for treating other viral infections *via* oromucosal administration of other interferons. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).<sup>1</sup>

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

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wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of viral infections, including hepatitis, HIV, herpes, and influenza comprising oromucosal administration of an interferon.

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<sup>1</sup> As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

In the instant case, the claims recite limitations wherein the interferon administered *via* oromucosal contact "does not involve direct action of the interferon on virally infected cells" and wherein "biologically active interferon does not enter the bloodstream". If a patient has, for example, hepatitis, it is not at all clear how such an infection could be treated if interferon does not act on the viral cells and does not enter the blood stream. For example, Smith *et al.* (Antiviral Res., 1987, Vol. 8, pages 239-245) teach that intranasally administered interferon,



while preventing hepatitis virus from extending from the nose to the brain, does not protect against dissemination of virus to other organs. Further, and more importantly, systemic infection was not affected by intranasal interferon treatment (Abstract). Hayden *et al.* (Antimicrobial Agents and Chemotherapy, 1988, vol. 32, no. 2, pages 224-230) teach that intranasal administration of 10-MU/day or 20-MU/day of interferon- $\alpha_{2b}$  is not effective in treating naturally occurring common colds (Abstract). However, Hayden *et al.* (J. Infect. Dis., 1984, vol. 150, no. 2, pages 174-180) teach that intranasal administration of 27-MU/day interferon- $\alpha_2$  for five days is marginally effective in treating rhinoviral infections. As such, it appears to be entirely unpredictable whether a high dose of oromucosally administered interferon, which does not directly affect viral cells and does not enter the bloodstream as a biologically active agent, will have any beneficial effect in treating any and all viral infections, especially systemic viral infections. Further still, U.S. Patent No. 7,267,827 issued to Santus *et al.* teaches that many therapeutic agents cannot be nasally administered. While Santus *et al.* do teach that B-interferon in a “special formulation” has proved suitable for nasal administration, in general, Santus *et al.* state that “the ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes” (col. 2, lines 51-67).

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the general treatment of any and all viral infections *via* oromucosal administration of any and all interferons. While the claims

recite doses of interferon, the dose is only indicated to be “greater than” a given amount and is not limited to any particular interferon or viral infection.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens or interferons necessary to treat all of the various viral infections claimed, particularly in humans. The direction concerning treating viral infections is found in the specification at pages 21-22, which merely shows that interferon- $\alpha$  administered oromucosally to mice protected the mice from an EMCV infection. However, there is no data relating to the treatment of any previously established viral infections. Applicant describes formulations at page 13. Doses required to practice the invention are described at page 8. With respect to dose, it is only disclosed that the dose is greater than  $0.28 \times 10^6$  IU/kg body weight and preferably greater than about  $30 \times 10^6$  IU. There are no guidelines for determining the doses needed to treat a hepatitis infection vs. a rhinovirus infection vs. an HIV infection via oromucosal contact of an interferon. Are the identical doses to be used for treating these unrelated viruses? There is an *in vivo* assay described in pages 21-22 but it is unclear if this assay correlates to the *in vivo* treatment of all viral infections with all interferons as encompassed by the claims. There is no working example demonstrating the treatment of any viral infections in animals or man. The lethal challenge EMCV (encephalomyocarditis virus) assay (pages 21-22) provides evidence that interferon- $\alpha$  protects mice from getting an EMCV infection. However, protection against infection does not predictably correlate to treatment of an established infection. For example,

while vaccines may protect one getting an infection or disease, once the infection or disease is established, vaccines are generally useless as therapeutic treatments. Thus, there are no working examples correlating protection against an EMCV infection with efficacy in the treatment of viral infections using any and all oromucosally administered interferons.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that oromucosal administration of interferons could be predictably used as a treatment for all viral infections as inferred in the claims and contemplated by the specification.

*Genentech Inc. vs. Nova Nordisk* states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicant has presented a general idea that because interferon- $\alpha$  when administered oromucosally protects mice from an EMCV infections then all oromucosally administered interferons must therefore, *a priori*, be useful in the treatment of all viral infections. However, the claims encompass a multitude of different interferons and pathologically distinct viral infections. Applicant tested one interferon for activity in protecting mice against one type of viral infection.

Determining if any particular claimed interferon would treat any particular viral infection would require isolation and purification of the interferon, formulation it into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical

efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicant. For example, *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy. Further, because the claimed methods require the treatment of a patient *via* administration of interferons through a specific route of administration, to test the efficacy of the claimed methods necessarily requires *in vivo* animal testing or human clinical trials. *In vitro* screening methods cannot be used to determine which interferons might be effective in treating any particular viral infection via oromucosal administration.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success. While the skilled artisan would reasonably expect a rhinoviral infection to be treatable *via* oromucosal contact of an interferon (see references discussed below), the skilled artisan would not reasonably expect any and all systemic viral infections to be treatable *via* a method of administration that leads to biologically active interferon not entering the bloodstream and not acting on virally infected cells.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/James D Anderson/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614